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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/042,583	03/17/98	NI J	PF366

HM12/1106
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EXAMINER	
KAUFMAN,C	
ART UNIT	**PAPER NUMBER**
1646	17

DATE MAILED: 11/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/042,583	Applicant(s) NI, ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *24 July 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *60,79,150,167,203 and 223* is/are withdrawn from consideration.

5)☒ Claim(s) *35-52,54-59,61-84, 86-89,91-99,102-105,107-113,115-117,120-123,125-149,151,153, 155-159, 161-166,168-169,176-179, 181-189,192-195,197-202,204-209, 212-215 and 217-222, 224* is/are allowed.

6)☒ Claim(s) *53, 90, 100, 106, 114, 118, 124, 152, 160, 180, 191, 196, 211, 216, 225, 226, 230-244, 247-256, 270, 271, 273-286* is/are rejected.

7)☒ Claim(s) *227-229, 245-246, 272* is/are objected to.

8)☒ Claims *pending* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *24 July 2000* is: a)☒ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

U.S. Patent and Trademark Office
PTO-326 (Rev. 3-98) **Office Action Summary** Part of Paper No. 17

Continuation of Disposition of Claims: Claims pending in the application are 35-61, 79, 81-84, 86-100, 102-118, 120-153, 155-169, 176-189, 191-209, 211-286.

DETAILED ACTION

The amendment filed 7/24/00 has been entered.

Continued Prosecution Application

The request filed on 7/24/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/042,583 is acceptable and a CPA has been established. An action on the CPA follows.

Receipt is acknowledged of the statement requesting that Jeffery Su be deleted as a named inventor which was filed with the Continued Prosecution Application (CPA) on 7/24/00. The inventorship has been corrected as requested.

Election/Restrictions

Applicant's election with traverse of claims 60, 79, 150, 167, 203 and 223 in Paper No. 16 is acknowledged. The traversal is on the ground(s) that the publications that disclose host cells comprising TNF-family receptors normally also disclose that such host cells are useful to screen for ligand binding and so the search of those claims would not present a serious burden. This is not found persuasive because as stated in the previously Office action, the method is classified differently from the host cell, nucleic acid and protein (435/7.2) and requires a different search than that required for the nucleic acid, vector and host cell. Publications disclosing host cells will not necessarily disclose ligand screening assays because host cells are often exclusively used for the amplification of nucleic acid and simple production of protein without screening assays set forth. For example, the GenBank reference relied upon in the rejection below teaches a host cell with no ligand binding. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Response to Arguments

The rejection of claims under 35 USC 102 and 103 is withdrawn in view of the amendment to the claims. Note that a new rejection under 35 USC 102 appears below.

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims. Note that a new rejection appears below.

The rejection of claims under 35 USC 112, first paragraph, is withdrawn in view of the amendment to the claims. Note that a new rejection appears below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 279 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It appears that claim 279 was intended to depend from claim 270 instead of cancelled claim 170. As a result, it has been examined as if depending from claim 270; however, applicant must make appropriate corrections to the claim.

Claims 227-229, 245-246 anf 272 are objected to for depending on rejected claims.

Claim Interpretation

Claim 270, which recites "An isolated polynucleotide comprising a nucleic acid which encodes a polypeptide at least 90% identical to 50 contiguous amino acids within amino acids 1 to 360 of SEQ ID NO:2" is being interpreted by the examiner as meaning 90% identical over the entire 50 contiguous amino acids. Therefore, polypeptides a long as 55 and as short as 45 amino acids are encompassed, but not, for example, a 400 amino acid-long fragment polypeptide that comprises a fragment at least 90% identical to 50 contiguous amino acids within amino acids 1 to 360 of SEQ ID NO:2. The examiner's interpretation seems consistent with, for example, dependent claim 273 which recites "wherein said nucleic acid encodes a polypeptide fragment capable of functioning as part....". With the examiner's interpretation, it is clear what is

encompassed by the encoded polypeptide fragment. If Applicants disagree with this interpretation, then the claim will be subject to a rejection under 35 USC 112, second paragraph, that will not be a new grounds of rejection as the issue has been raised herein.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 53, 90, 100, 106, 114, 118, 124, 143, 152, 160, 180, 191, 196, 211, 216, 234, 251, 264, 273, 274 and 279 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 100, 114, 118, 152, 191, 211, 273 and 274 are indefinite because it is unclear what is meant by " a polypeptide fragment which is capable of functioning as part of a mature DR5 polypeptide to induce apoptosis." It is unclear what the relationship of the fragment is to the mature DR5 polypeptide. For example, it is unclear if it is intended that the fragment replaces a corresponding section of a mature DR5 polypeptide so that it is embedded within the remaining portion(s) of the DR5 polypeptide, or if the fragment binds to or otherwise interacts with a mature DR5 polypeptide so that apoptosis is induced.

Similarly, claim 273 is indefinite because it is unclear what is meant by "a polypeptide fragment which is capable of functioning as part of a DR5 extracellular domain to bind TRAIL." The intent of the meaning of "functioning as part of...." is unclear for the reasons set forth in the preceding paragraph.

Claim 53, 90, 106, 124, 143, 160, 180, 196, 216, 234, 251, 264 and 279 are indefinite because it is drawn to producing a vector, yet the starting material is a vector. This method is then circular and one does not produce anything.

Claim Rejections - 35 USC § 112, First Paragraph

Claim 286 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a polypeptide that is at least 90% identical to 50 contiguous amino acids within amino acids 1-360 of SEQ ID NO:2 wherein said polypeptide is specifically bound by an antibody that also specifically binds the corresponding region of said 50 contiguous amino acids of SEQ ID NO:2, does not reasonably provide enablement for a

polypeptide that cannot be bound by such an antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not teach how to use a polypeptide that is structurally only required to comprise a fragment 90% identical to 50 contiguous amino acids of SEQ ID NO:2, if that polypeptide cannot be used to make an antibody to the naturally occurring DR5 sequence (*i.e.*, SEQ ID NO:2). One would not reasonably expect that a fragment with 45/50 amino acids in common with SEQ ID NO:2 to have any property of the full length disclosed DR5 receptor or the full ECD (extracellular domain) or ICD (intracellular domain) thereof. The ECD is 133 amino acids long and there is no showing or reasonable expectation that a fragment of 45-50 amino acids is sufficient to bind a ligand since binding is a complex stereochemical event. Nor is there any showing or reasonable expectation that such a fragment is sufficient to induce apoptosis since the domain responsible for transducing the apoptotic signal is 202 amino acids long (see Figs. 1A-B), again because of the complexity of interactions required for the event to occur. Also, while the specification says fragments of SEQ ID NO:2 can be used to produce antibodies that bind DR5, antibody epitopes are dependent on 3-dimensional structure of the protein and it is unpredictable if an antibody made to a 45-55 amino acid-long fragment that is not identical to a similar fragment of SEQ ID NO:2 would produce a protein that bound the disclosed DR5 of SEQ ID NO:2. If the antibody did not, one would not know how to use the antibody made to the non-identical fragment. For these reasons, the method of producing the encoded polypeptide is enabled only if the polypeptide made is enabled. Note that the encoding polynucleotide is enabled because even if it is not 100% identical to SEQ ID NO:1, it would reasonably be expected to function as a probe that could be used to detect the polynucleotide of SEQ ID NO:1.

Claim Rejections - 35 USC § 102

Claims 225, 226, 230, 231, 234-240, 242-244, 247, 248, 251-255, 270, 271, 273-276 and 279-285 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AA223122 (V).

GenBank Accession No. AA223122 teaches a polypeptide that is 97% identical over

nucleotides 236-698 of SEQ ID NO:1 of the instant specification (see "SEQUENCE COMPARISON-B" of paper #6). This region comprises the nucleic acid capable of encoding a contiguous stretch of 138 amino acids at least 97% identical to the corresponding stretch of SEQ ID NO:2 of the instant application, which is encoded by a nucleotide beginning at about position 282 of SEQ ID NO:1 for the mature polypeptide. Therefore, this polynucleotide encodes a polypeptide fragment capable of functioning as part of DR5 ECD to bind TRAIL as well as part of a mature DR5 to induce apoptosis. The nucleic acid is in the Bluescript SK- vector. This vector inherently has the property of being operably linked to a heterologous regulatory sequence (*i.e.*, T3 or T7 promoter) and comprises a heterologous polynucleotide which encodes a heterologous polypeptide, *i.e.*, β-galactosidase. The vector is in the SOLR host cell (see "Source" section). Because of the length and high identity of the nucleic acid of AA223122, one would reasonably expect that it encodes a polypeptide fragment that binds an antibody with specificity for the polypeptide of SEQ ID NO:2. Note, claim 242 is a polynucleotide comprising a nucleic acid which encodes a polypeptide selected from the group, so the GenBank polynucleotide meets that limitation.

Claim Rejections - 35 USC § 103

Claims 225, 226, 230-244, 247-256, 270, 271 and 273-286 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. AA223122 (V) and Chinnaiyan et al. (Science, 1996, cited by Applicants), Sibson et al. (WO 94/01548, N), and Bjorn et al. (V, Current Biol., 1992) in view of Adair et al. (O, WO 91/09967).

GenBank Accession No. AA223122 teaches a polypeptide that is 97% identical over nucleotides 236-698 of SEQ ID NO:1 of the instant specification (see "SEQUENCE COMPARISON-B" of paper #6). This region comprises the nucleic acid capable of encoding a contiguous stretch of 138 amino acids at least 97% identical to the corresponding stretch of SEQ ID NO:2 of the instant application, which is encoded by a nucleotide beginning at about position 282 of SEQ ID NO:1 for the mature polypeptide. Therefore, this polynucleotide encodes a polypeptide fragment capable of functioning as part of DR5 ECD to bind TRAIL as well as part of a mature DR5 to induce apoptosis. The nucleic acid is in the Bluescript SK- vector. This

vector inherently has the property of being operably linked to a heterologous regulatory sequence (*i.e.*, T3 or T7 promoter) and comprises a heterologous polynucleotide which encodes a heterologous polypeptide, *i.e.*, β-galactosidase. The vector is in the SOLR host cell (see "Source" section). Because of the length and high identity of the nucleic acid of AA223122, one would reasonably expect that it encodes a polypeptide fragment that binds an antibody with specificity for the polypeptide of SEQ ID NO:2. The nucleic acid is classified as an EST (see "Division Code"). GenBank Accession No. AA223122 does not teach production and recovery of an encoded polypeptide or fusion to a polynucleotide encoding a human immunoglobulin Fc region (Ig-Fc).

Chinnaiyan et al. teach vectors comprising the DR3 receptor-encoding nucleic acid, transfection of mammalian cells, and expression followed by recovery of the receptor by FLAG immunoprecipitation (see legend of Figure 3B). It was also shown that without the death domain, DR3 blocked DR3-induced apoptosis (Chinnaiyan et al., p. 992, first paragraph).

Sibson et al. teach the desirability of expressing ESTs. It is stated (p. 10, line 38) that "Partial or full length cDNAs have great utility once expressed." And (p. 11, lines 9-10), "The proteins thus-expressed can be screened for activities of therapeutic or commercial value." Also taught is that fragments as short as 8 amino acids in length can be used as antigens for the production of useful antibodies (p. 11, lines 16-22). Also taught is an EST library formed by ligating each DNA piece into a pBluescript vector and transformation of *E. coli* host cell DH5a (p. 19, third paragraph). All methods of expression described by Sibson et al. are old in the art (*e.g.*, p. 8, lines 26-34).

Bjorn et a. teach the advantages of fusion proteins comprising Ig-Fc. On page 571, third paragraph, it is stated that "Capon and co-workers [10] showed that by fusing the CD4 derivative to the Fc portion of immunoglobulin G (IgG), the serum half-life of CD4 in rabbits increased 200-fold. This result demonstrates that a rapidly cleared protein can be stabilized by fusion to a carrier which is more stable *in vivo*."

Adair et al. teach humanized antibodies and that non-human antibodies are antigenic in humans and lead to an undesirable immune response (p. 2, beginning of third paragraph).

It would have been obvious to express and recover the polypeptide encoded the nucleic acid of GenBank Accession No. AA223122 because Chinnaiyan et al. teach methods of

expressing nucleic acids and recovering the products, and Sibson et al. also teach methods as well as the desirability of obtaining such expressed polypeptides, for example for use as antigens. If further would have been obvious to produce the encoded protein as fused to a human Ig-Fc region because Bjorn et al. teach this increases the half-life of the non-Fc protein and Adair et al. teach that using human Ig-Fc will not lead to an undesirable immune response in humans. This would be desirable if one sought to use the DR5 polypeptide without the death domain as a means to inhibit apoptosis in humans as suggested by Chinnaiyan et al. for the function of the DR3 deletion construct used *in vitro*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

November 3, 2000